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An overview of the epidemiology, transmission, pathogenesis and treatment of scabies

EDUCATION

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ABSTRACT

Summary

Scabies is a well-known, yet a poorly understood neglected tropical disease (NTD). Although less common in the UK, scabies epidemics regularly occur abroad, in tropical, less developed communities (LDCs). Cases are prevalent in communities which tend to live with overcrowding, poor sanitation and limited access to healthcare facilities and medication. This environment provides the perfect breeding ground for the growth and the transmission of scabies. The body has a delayed response to infestation – this is due to the scabies mites' ability to disrupt the complement cascade and delay the onset of the adaptive arm of the immune response.

Relevance

Contrary to popular belief, anyone can become infested with scabies. Although not usually life-threatening, scabies can cause unpleasant symptoms as well as worsen existing skin conditions, which can reduce a person's quality of life. Prompt diagnosis is challenging in LDCs. Undiagnosed scabies may lead to serious complications such as secondary skin sepsis as well as allowing further transmission. Scabies is highly contagious; clinicians should be aware how to spot and treat scabies early on, and additionally know to offer treatment to other individuals that the patient has been in close contact with.

Take Home Messages

Management for scabies is relatively simple and involves the application of topical medication, such as Permethrin. Despite this, there are still many barriers to treating epidemics in LDCs, such as a lack of access to treatment and healthcare professionals, a lack of awareness from clinicians about the condition's clinical manifestations, as well as lack of infrastructure to definitively diagnose the condition. Despite progress in management of the condition, the pathophysiology and transmission of the condition are only partly understood, and the rise of resistance to current scabicides is indicative of the need for newer treatments, especially within resource-poor communities.

INTRODUCTION

The World Health Organisation (WHO) defines neglected tropical diseases (NTD) as 'a diverse group of communicable diseases that prevail in tropical and subtropical conditions in 149 countries.' (1) It is currently estimated that NTDs affect over 1 billion people, the majority of which live in less developed communities (LDCs), which have a lack of sanitation and healthcare access. This lack of access facilitates the spread of communicable diseases, potentially leading to preventable complications, such as blindness, physical deformities, and neurological problems. (2) The grouping of NTDs has led to their increased awareness amongst clinicians and has provided a compelling platform to derive specific management plans. Recent evidence has suggested that investments addressing NTDs is cost-effective for developing economies. More people cured will ensure a larger, healthier work force, consequently boosting the economy of developing nations. (3)

There are currently 17 NTDs including the well-known skin disease scabies. Skin diseases are one of the most frequent reasons for GP consultation. Skin diseases represented 8.4% of German consultations in 2010, with this set to increase globally. (4) Most patients with dermatological problems are only treated by their GP and are not referred further. (5) Although the prevalence of scabies in the UK is low, the condition still has global importance. Therefore, all clinicians should be aware of scabies, as well as understand how to diagnose and treat it, due to its profound impact on the skin. Skin protects internal organs, thermoregulates, allows sensation, forms vitamin D and therefore regulates calcium and phosphate levels in the body, acts as a physical barrier to the entry of foreign substances/ pathogens and is aesthetically important. (6)

Scabies is defined in two major forms, ordinary scabies (OS) and the more severe, crusted scabies (CS). (7) Both manifest from the same species of mite, thus management and treatment are largely the same between the conditions. This piece aims to discuss the epidemiology, transmission, clinical manifestation, and the pathophysiology of scabies, as well as the body's subsequent immunological response to the disease. In addition, this piece will describe the use of mass drug administration (MDA) as a treatment in LDCs with a scabies endemic, before briefly outlining the future of the methods of diagnosis and management of scabies.

Epidemiology

Scabies predominantly affects children and the elderly in the developing world, regardless of gender or race. Regions with the highest prevalence of scabies include India, the South Pacific and Northern Australia (which includes the Aboriginal community, which has the highest prevalence for CS). Communities based in these densely populated, tropical areas tend to live with overcrowding, poor sanitation and limited access to healthcare facilities and medication. This environment provides the perfect breeding ground for the growth and the transmission of scabies. (9, 10) In the UK, members of lower socioeconomic households/communities are more likely to experience some of the effects of relative poverty. These effects

include inadequate access to health facilities and treatment, a poor level of hygiene, the sharing of unclean clothing, bedding or towels may facilitate transmission of scabies, malnutrition, and illiteracy. In addition, frequent population movements also facilitate the spread of the infestation. Though the exact prevalence of CS is unknown, it is thought to be rare; however, on several occasions, local epidemics of OS have originated from a single case of CS. (11)

There is a notable correlation between overcrowding and the prevalence of scabies. Overcrowding facilitates the rapid spread within a population. (10, 12) Additionally, the cases of scabies fluctuate depending on seasonal changes. A Russian study found that between the months of September and December, the fertility of scabies mites (and thus the incidence of scabies) was greater compared to the months of January to July (fertility index scores of 11.5 versus 8.9, respectively). (13) Further findings exemplified that scabies mite oogenesis arrest tends to be greater during the former half of the year, which subsequently leads to a seasonal decrease in the local scabies mite population which may cause a decreased incidence of scabies over the summer period. (13, 14) Finally, it is also important to note that a lack of healthcare and education regarding the condition and general hygiene inevitably mean that cases go untreated, contributing to its transmission and prevalence.

In the UK, the overall prevalence of scabies is 2.81 per 1,000 females and 2.27 per 1,000 males. Although relatively uncommon, children between the ages of 10 and 19 experience the highest infestation rates. There is a significantly greater infestation rate among females with a relative risk of 1.24 ($p < 0.001$) compared to males. (15)

Transmission

Scabies is a parasitic infection, caused by *Sarcoptes scabiei* var *hominis* (*S. scabiei*). These mites burrow into the stratum corneum of the epidermis of the skin, where the microenvironment is ideal for the parasite to remain and lay its eggs. This subsequently leads to an immune response from the host. This process is summarised in Figure 1.

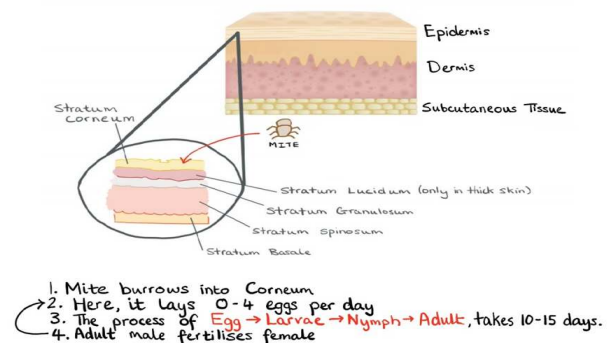
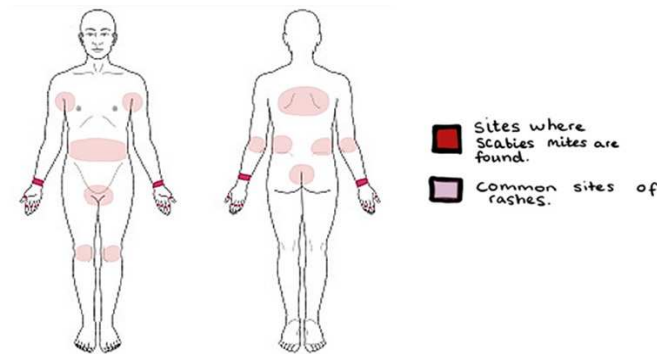


Figure 1:

The life cycle of *S. scabiei* and an illustration of the layers of skin and epidermis.

**Figure 2:**

Common sites *S. scabiei* mites are found, as well as sites of rashes.

Common sites of rashes and mite habitation can be seen in Figure 2; it includes areas such as the groin, shins, and armpits. (16) Extensive skin-to-skin contact with a person who has scabies is the most common form of transmission. Transmission may also occur via contact with items such as clothing, bedding, or towels that have been used by a person with scabies (more common in CS), or by having sexual intercourse with someone with the disease. (17) Based on this, it is understandable why those in LDCs experience the highest rates of prevalence, as transmission is exacerbated by overcrowded conditions that people may live in, as well as a general lack of sexual health awareness that may contribute to the spread of disease. Within 15 to 20 minutes of exposure, *S. scabiei* can infiltrate the skin and subsequently initiate its life cycle. The time taken for the onset of clinical manifestations after initial exposure may be up to eight weeks. (16) A correct diagnosis may be further delayed due to a lack of awareness from clinicians, as the signs and symptoms of scabies can mimic several other forms of skin disease, leading to a misdiagnosis. Further barriers to a rapid diagnosis include the lack of access to a hospital/GP and a lack of equipment that some practices may have to examine the patient. (18)

Clinical Manifestation and Diagnosis

One of the first symptoms of OS is a rash at the sites shown in Figure 2, and an intense pruritus, which typically worsens at night. At early stages of the condition (when scabies mites lay eggs in the skin), silvery lines with a dot at one end can be seen on the skin. As the rash spreads, it begins to present as tiny red spots. (17) A rash and pruritus are normally absent in CS; CS presents differently in that it presents more severely. There are many more mites in the skin, leading to CS being typically characterised by thick crusts of the skin, with a grey discolouration. (19) In CS, breached areas of the skin may exhibit erythema, which predisposes patients to secondary bacterial infection from *Staphylococcus aureus* and *S. pyogenes*, (20) as well as causing skin infections like impetigo and worsening any existing eczema or psoriasis. (17)

Diagnosis of scabies is usually based on the history of the presenting symptoms. It is important to also take a social and family history in these cases, so that clinicians may understand if the condition has been spread via a family member. The presence of mite burrows in the skin are infrequently seen in OS, (7) so doctors may use other methods to achieve a definitive diagnosis. Methods may include dermatoscopy, but due to the equipment required this is infeasible in many remote areas, or a skin scrape, which involves scraping a blade coated with oil across a burrow and then examining the collected sample microscopically. Finally, scabies could also be diagnosed in remote communities via a 'burrow ink test': a lesion suspected to be caused by scabies is covered in ink and then rubbed off the patient using alcohol. For a scabies-positive result, an ink tracking would remain in the burrows. (7)

Pathogenesis

Innate, humoral, and cellular responses are thought to play a significant role in the body's response to scabies. The immunological response is more apparent in patients with CS compared to OS, as the high mite count proportionally induces a stronger response. (21) A sufficient immune response is only generated 4–6 weeks after initial contact is made, partly due to genetic changes involved in epithelium development and partly because of the mite's ability to modulate gene expression via the expression of inhibitor proteins, thus delaying an innate immune response. (22) Once detected however, the body can overcome the condition, with assistance from medication. On the other hand, the doctor should feel the patient is sufficiently informed of the above to make a personalised decision. They should appreciate what the patient would consider a good outcome. They should understand what risks are important to that patient. They should have taken the opportunity to apply these factors to their recommended management plan. They should understand why a patient has come to a particular decision.

Innate immune response

The *S. scabiei* present in the stratum corneum is detected by two of the three complement-activating pathways: the classical and alternate pathway, which are activated by antigen-antibody complexes and endotoxins. (23) This leads to activation of the complement cascade, which produces the compounds C3a, C3b, C4a and C5a. The formation of these compounds eventually leading to the following outputs: chemotaxis of neutrophils and eosinophils to the parasite, mast cell activation, cell lysis and opsonisation of the parasite, which makes it more vulnerable to destruction by the immune system. The overall effect of these outputs is the priming of an adaptive immune response, which includes the mobilisation of a high number of eosinophils (responsible for the anti-helminth response) towards *S. scabiei*. When several of these eosinophils attach to the mites, they release compounds such as peroxidase, ribonuclease, and major basic protein, all of which contribute to killing the mites and their eggs. (24) *S. scabiei* have evolved to evade the complement cascade, via the production of two proteins: scabies mite serine protease inhibitor B3 and 4 (SMSB3 and SMSB3). (25) Both proteins bind directly to complement proteins, inhibiting their action in a way that all three complement-activating pathways are

disrupted. (26) This results in a temporary delay in the recruitment of eosinophils and a delay in the activation of the adaptive immune response. Consequently, *S. scabiei* can survive and multiply in the host longer.

Adaptive immune response

The adaptive immune response must be launched to allow a host to overcome scabies. The role of the adaptive immune response becomes apparent when the numbers of Th2 lymphocytes increase in response to the parasite. The Th2 cell in turn secretes interleukins 4, 5 and 13 (IL-4, IL-5 and IL-13). Among other things, IL-4 promotes class switching of antibodies produced by plasma cells into different isotypes, notably, immunoglobulin E (IgE). IL-5 promotes the recruitment of eosinophils towards the site of infection, and IL-13 is responsible for expelling the parasite from the body once it has been killed. (27) There is an association between the presence of scabies and increased levels of antigen-specific IgE. (28)

IgE is a glycoprotein that specifically binds to target parasitic antigens. Effector functions of the antibody are normally mediated via the fragment crystallisable (Fc) region. It is this region which the eosinophils bind to, using the Fc ϵ RI receptors on their surface. Only when this binding occurs can the eosinophil begin to act on the parasite to kill it. (29) The antigen-binding fragment (FAB) of IgE binds to the corresponding receptor antigen on *S. scabiei*. Its high affinity results in numerous IgE antibodies coating *S. scabiei*. This is summarised in Figure 3. The interaction between the innate immune system and the humoral arm of the adaptive immune system allows the body to overcome the infestation.

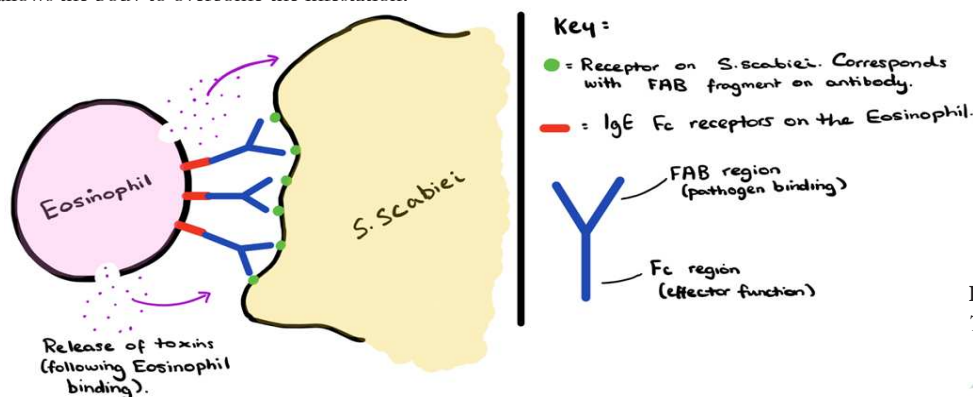


Figure 3:
The effector function of IgE.

The WHO recommends mass drug administration (MDA) as a method to treat and control outbreaks of scabies in LDCs. MDA involves treating every member within a defined population and location (unless specifically contraindicated) with scabicides, without individual diagnosis. In endemic areas, it aims to reduce transmission and alleviate symptoms of those infested. (32) A study conducted in rural Fiji tested the effectiveness of MDA, using Permethrin as medication. The trial was conducted in 2012 for 12 months and involved 2051 participants in total. It found that those who underwent MDA had a statistically significant 62% reduction in cases of scabies from baseline. (33) Though this study, along with others, suggest that MDA is effective in LDC, a limitation to this model regards population movement between an area which had been treated with MDA to scabies-prevalent areas, which may lead to re-infestation.

As mentioned above, there are several difficulties in promptly diagnosing scabies in LDCs. However, recent advancements in diagnosis may assist this issue. A study by Jayaraj and colleagues investigated the potential of using IgE antibodies which are specific to recombinant Sar s 14.3 (rSar s 14.3), a major antigen of scabies. This immunological assay was quantified and assessed. The diagnostic efficiency of rSar s 14.3 detecting active scabies infestation was extremely high, with a 100% sensitivity and 93.75% specificity to patients with scabies. This shows great potential as a test for scabies. (34) Nonetheless, it is still in its early stages of development, and appears to be resource intensive, which may be a problem for resource deficit countries.

CONCLUSION

Scabies has been brought back to the attention of clinicians worldwide when the WHO categorised it as one of 17 NTDs. Although not usually life-threatening, scabies can cause symptoms which can reduce a person's quality of life. Undiagnosed, scabies may lead to serious complications such as secondary skin sepsis, as well as devastatingly vast transmission in densely populated areas. Problems in LDCs include the difficulty surrounding diagnosis due to a lack of awareness about the condition, as well as the scabies mite's adaptations to evade the immune system. Despite progress in the management of the condition, the pathophysiology and transmission of the condition are only partly understood. The rise of resistance to current scabicides is indicative of the need for newer treatments, especially within resource poor communities.

Treatments and further developments

In the UK, the two most widely used treatments for scabies are Permethrin and Malathion. Both medications are to be applied topically and contain insecticides that kill the scabies mite. Of the two medications, Permethrin 5% cream is usually recommended as the first-line treatment; Malathion 0.5% lotion is administered if permethrin is ineffective. (30) Clinicians ask patients to apply the medication to their whole body, from the neck down, and leave it on for at least 8–10 hours (some treatments may also require a second application). (31) Clinicians should also recommend treatment for all the people the patient has been in close contact with, even if they show no signs of scabies infestation; this is due to the contagious nature of the condition.

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